I do wonder about an alternative to my career (or, instead, to the peer-review system, not sure which of the two would be easier).

***What is your favourite/least favourite conference?*** I was inspired by the Cold Spring Harbour Meetings on Human Evolution and Disease in the 1990s which brought together the scientific world elite from various fields of human evolution. Unfortunately, dedicated conferences that include specialists from different fields working on human evolution such as palaeontology, archaeology, linguistic, biological and cultural anthropology are rare. Although it is not always easy to find a common language between people of such diverse disciplines, it is possible. I know this from my time at the Max Planck Institute for Evolutionary Anthropology in Leipzig, where such an interdisciplinary approach to human evolution is practised with great success.

***Do you have a 'scientific hero'?*** I don't really have a scientific hero. However, I do esteem (and prefer collaborating with) colleagues who manage to be both good scientists as well as good human beings (in contrast to the turbo-capitalists in science who are successful to the disadvantage of others). A good example for the former is Mark Stoneking whom I have had the privilege to work with for many years already and hopefully many more to come.

***What do you think about electronic publishing?*** I think e-publishing is great, simply because it allows speedy publication, and I am actively supporting it as Co-Editor-in-Chief of the new e-journal *Investigative Genetics*. Everyone of us knows that desperate feeling of waiting weeks or months until an accepted paper gets finally published (and the pain of getting scooped at the very last moment). Indeed, I now prefer to look at papers online instead of final issues of journals, and almost never look at print issues anymore. I know some still prefer having a printed journal, but I believe that the advantage of speedy publication outweighs nostalgic feelings towards the printed page. I also value open-access publishing for a wider distribution of scientific knowledge, and actively support it, as an Academic Editor of *PLoS One*. However, I also see the advantage of having professional copy editors: they can make the life of an author easier, especially for us non-native English speakers.

***What is your greatest ambition in science?*** We all know that genetics must play a major role in the determination of human facial appearance, because monozygotic twins look identical, at least for parts of their life. However, although we are constantly accumulating genetic knowledge for many human diseases, we know almost nothing yet about the genes determining facial appearance. I would like to find out — or at least contribute to finding out — which genes determine human facial morphology. For instance, I am co-chairing the international VisiGen consortium aiming to find genetic factors that determine human visible traits. To me, this is fascinating not only because of the general scientific interest but also because it may provide future forensic applications.

***What do you think are the big questions in your field?*** Currently, my favourite question in forensic molecular biology is to what degree it will be possible to estimate human appearance from biological samples found at crime scenes. DNA-based appearance prediction is expected to provide investigative leads to find unknown individuals, who cannot be identified with current forensic DNA profiling techniques. At present, this is already feasible for some group-specific traits such as eye color. However, it really is individual-specific appearance (i.e. facial morphology), which would be of most use in the search for an unknown person, but where we lack almost any genetic insights thus far. In human evolutionary genetics, an exciting question is how humans genetically adapted to their environment. Some genes have already been identified that contribute to certain phenotypes and carry strong signatures of positive selection, such as those involved in skin color variation. However, many more human traits are expected to be determined by environmental interactions and it will be fascinating to establish genetic (and ultimately functional) evidence for these.

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## Quick guide

# Kindlins

**Mohamed Bouaouina and David A. Calderwood**

***What are kindlins and why are they getting so much attention?*** Kindlins are evolutionarily conserved, FERM-domain-containing adaptor proteins important for signaling to and from integrin adhesion receptors. In mammals, the kindlin family comprises kindlin-1, -2 and -3, each encoded by a different gene. *Drosophila* have two kindlins (fermitin-1 and -2), while *Caenorhabditis elegans* has only one (UNC-112). Although only recently identified, in the past three years there has been a surge of interest in kindlins, spurred by the finding that kindlin mutations trigger human disease, by the unique organization of the kindlin FERM domain and, most notably, by the realization that kindlins play essential roles in regulation of integrin activation. This final point is supported by data from knockout animals, disease mutations, and overexpression studies and is noteworthy because previously the only well-recognized, direct integrin activator was talin, a kindlin-related, FERM-domain-containing, integrin-binding, adaptor protein. Mechanistically, how kindlins act remains unknown, but improved understanding of kindlin structure, function and interactions is likely to reveal where kindlins fit into the process of talin-mediated integrin activation and how integrin–kindlin interactions regulate adhesion signaling.

***Where does the name come from?*** The various routes by which kindlins were identified are reflected in their alternative names. The first indication of a role for kindlins in integrin-mediated adhesion came from genetic screens in *C. elegans*, in which UNC-112 was identified as an essential intracellular protein that localizes at cell–matrix adhesion structures. Human kindlin-1 and -3 were originally named UNC-112-related proteins-1 and -2, while kindlin-2 was cloned as mitogen-induced gene-2. Kindlins are also called fermitin family homologs, for their homology with *Drosophila* fermitins, whose name reflects the importance of the FERM domain in these proteins. However, the

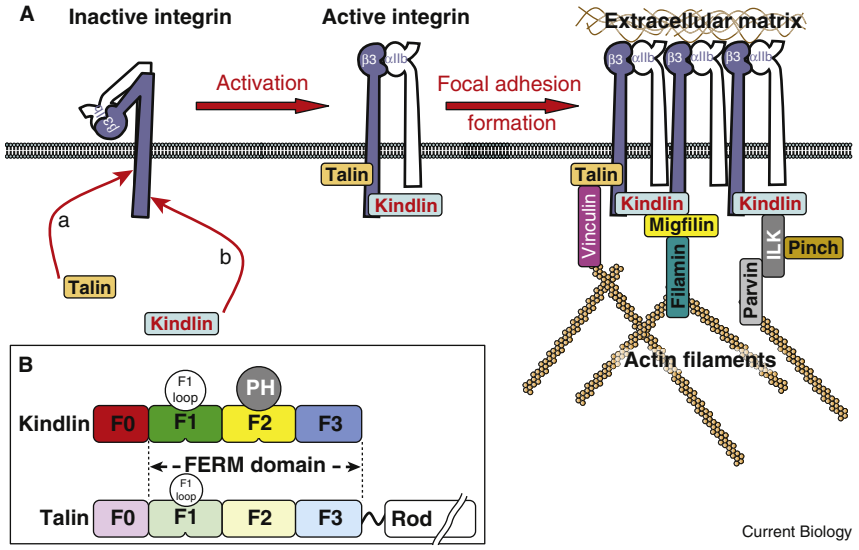


Figure 1. Kindlin interactions in integrin activation and signaling.
(A) Binding of kindlin to the cytoplasmic tail of the β3 integrin enhances talin-mediated β3 integrin activation. The interaction order (a/b) is unknown. Active integrins, with high affinity for extracellular ligand, anchor the cell cytoskeleton to the ECM and form focal adhesions, multiprotein complexes involving kindlin and its partners. (B) Kindlin domain structure. Kindlin and talin share an atypical FERM domain not evident in other proteins.

widely accepted kindlin nomenclature is based on the finding that kindlin-1 mutations cause Kindler Syndrome (see below). Sequence similarity led to the naming of kindlin-2 and -3, although neither is directly implicated in Kindler syndrome.

***Where are kindlins expressed and what happens when they are missing?*** Kindlin-1 is expressed mainly in epithelia, particularly in basal keratinocytes, and, as mentioned, kindlin-1 mutations cause Kindler syndrome, which is characterized by skin blistering, atrophy, photosensitivity and occasionally ulcerative colitis. Likewise, the kindlin-1 knockout mouse develops skin atrophy and intestinal epithelial dysfunction. Kindlin-2 is ubiquitously expressed and its knockout is lethal, due to developmental arrest at the peri-implantation stage. Consistent with a widespread essential role for kindlin-2, no human diseases have been associated with germline kindlin-2 mutations. Kindlin-3 is generally hematopoietic, although it may also be expressed in endothelial cells, and kindlin-3 knockout mice provided the first definitive evidence that kindlins are important for regulating integrin activation. Kindlin-3-deficient platelets cannot activate the platelet integrin αIIbβ3 in response to normal cues and consequently cannot aggregate. Likewise, kindlin-3-deficient leukocytes exhibit defective activation of β1, β2 and β3 integrins and so fail to arrest and extravasate into inflamed tissues. These phenotypes are reminiscent of leukocyte adhesion deficiency syndrome type III and kindlin-3 mutations have now been shown to cause this syndrome.

***What do kindlins do?*** Kindlins lack enzymatic activity and are thought to function primarily as cytoskeletal scaffolds or adaptors. They localize to focal adhesions — multiprotein complexes of integrin adhesion receptors, cytoskeletal adaptors as well as signaling proteins important for adhesion signaling, organization of the actin cytoskeleton and assembly and remodeling of the extracellular matrix (ECM) (Figure 1). In *Drosophila* and *C. elegans,* kindlins cluster at muscle attachment sites, *in vivo* correlates of focal adhesions. Consistent with their subcellular localization, kindlins modulate signaling to and from integrins and loss of kindlins alters cell adhesion, shape and migration. Effects on integrin activation, most evident in kindlin-3-deficient cells and organisms, are also observed in kindlin-1- or kindlin-2-deficient cells, and overexpressed kindlins cooperate with talin to potentiate talin-mediated integrin activation. However, kindlins also have isoform-specific functions, as kindlin-2 cannot fully compensate for kindlin-1 in Kindler syndrome and may have integrin-independent roles in the nucleus and at cell–cell junctions.

***So what is integrin activation and why should we care?*** Integrins are a family of transmembrane, αβ heterodimeric adhesion receptors with large extracellular portions that bind ECM ligands and short cytoplasmic α and β tails that interact with cytoskeletal and signaling proteins. Integrins are essential for multicellular life and are tightly regulated by intracellular signals. These induce conformational changes in integrin extracellular domains that increase affinity for extracellular ligands, a process termed integrin activation. Integrin β tail binding to the FERM domain of talin triggers integrin activation; however, while talin is key to integrin activation, it is now evident that the kindlins can modulate this activity. Once activated, integrins bind extracellular ligands with high affinity, an event essential for platelet aggregation during blood clotting, leukocyte adhesion during host defense, cytoskeletal reorganization and spreading during migration and morphogenesis.

***How are kindlins involved in integrin activation?*** Kindlins are required for integrin activation because, even in the presence of talin, kindlin depletion impairs integrin activation. Alone, kindlins are not capable of robust integrin activation; indeed, overexpressed kindlins can inhibit activation. Co-expressing kindlins with talin enhances talin-mediated activation of the platelet integrin αIIbβ3, but inhibits the more widespread α5β1 integrin. The significance of this integrin specificity remains unclear but differential effects on β1 and β2 integrins have also been reported. Thus, the picture is still murky, but normal integrin activation requires kindlins and is sensitive to their underexpression or overexpression.

***How do kindlins impact integrins?*** Kindlins directly bind integrin β tails at a site adjacent to, but distinct from, the talin-binding site. This binding is required to enhance integrin activation. Whether talin and kindlin bind the tail simultaneously or successively, and whether a trimeric kindlin–talin–integrin complex is required for activation are unknown. Kindlins also bind other focal

adhesion proteins implicated in integrin activation, including integrin-linked kinase and the filamin-binding protein, migfilin (Figure 1). However, whether these interactions are important for activation or for kindlin-mediated integrin signaling, focal adhesion formation, and cell spreading is unclear and elucidation of the mechanisms of kindlin function will likely require detailed knowledge of its interactions.

***What about the kindlin FERM domain?*** Sequence analysis indicates that kindlins are composed solely of an atypical FERM domain. FERMs are widespread protein–protein interaction domains, typically composed of three subdomains (F1, F2 and F3) that assemble into a compact clover-shaped module. The kindlin FERM is most similar to that of talin, which is unusual in having an additional amino-terminal domain (F0), a large, flexible, membrane-binding loop in F1, and forming an extended structure rather than the compact one seen in all other FERMs to date (Figure 1). Like talin, kindlin contains an integrin-binding site within the F3 subdomain, but a unique and defining feature of kindlin FERMs is the insertion of a pleckstrin homology (PH) domain within an F2 subdomain loop, suggesting that phospholipid binding will be important for kindlin function. It is intriguing that kindlin and talin, two proteins intimately involved in integrin activation, both possess atypical integrin-binding FERMs. A deeper knowledge of the similarities and differences between talin and kindlin is likely to aid in understanding the molecular basis of kindlin activity and of integrin activation in general.

### *Where can I find out more?*

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**Primer**

# Polarisation vision

**Justin Marshall[1,*] and Thomas W. Cronin[2]**

Putting on a pair of polarised sunglasses is as close as most of us get to seeing polarised light. Photographers also use polarising filters and, in both cases, the reason for placing such filters in front of eye or camera is to reduce glare and increase contrast within the image or scene viewed. Animal visual systems also utilise polarised light for these purposes, along with navigation, sexual signalling and detecting water. They rarely, if ever, use optical filters to achieve polarisation sensitivity; instead it is an intrinsic property of their photoreceptors. Linear polarising sensitivity is common in the animal kingdom, particularly in invertebrates such as arthropods (insects, crustaceans and spiders) and cephalopods. Linear polarising sensitivity is also known in vertebrates, including fish, birds and a few amphibians and reptiles. In truth, this ability is probably more widespread than we think, and in the cephalopods and many crustaceans it may replace colour vision. While circular polarising photography — used for cancer detection in medical imaging and for (explosive) mine detection underwater — might be considered an obscure man-made optical trick, some animals also have circular polarising sensitivity. Before going on to describe how and why animals utilise polarised light, we briefly examine what polarised light is, why it is called linear or circular, where it comes from and where it is frequently found in natural environments (Figure 1).

**Polarised light and where to find it**

Polarisation can be confusing. Remember that light can be thought of as a wave as it propagates through space. The wavelength of light, measured in nanometres, is used to describe the spectrum, and in colour vision, animals are sensitive to different parts of this spectrum from the ultraviolet to far red (near 300 nm to over 700 nm). Colour vision requires at least two populations of photoreceptors sensitive to different parts of the spectrum plus a neural comparison of excitation between these to set up the sensation of colour. In polarisation, it is the electrical vector (e-vector) properties of the light waves that are significant. Polarising photoreceptors are often restricted in spectral sensitivity to around 380 nm on land and 500 nm underwater. Indeed, it is important that polarisation sensitivity does not confuse spectral variability with polarisation differences, and colour photoreceptors may deliberately destroy any intrinsic polarisation sensitivity that photoreceptors possess (Figure 2).

Light from the sun is unpolarised, producing e-vectors vibrating at all possible angles perpendicular to the direction of travel of the light beam (Figure 1). When this beam is scattered or passes through dichroic filters, in which some e-vectors are passed while others are absorbed, it becomes polarised. The end result is that most light now vibrates in a single plane, generally denoted by an angle relative to vertical. Dichroic filters wholly (100%) or partially polarise the light that passes through them, depending on the molecular nature of the filter material and the wavelength of the light. Thus, the angle of the e-vector and the degree of polarisation are important variables for polarisation sensitivity, the third being the intensity or brightness of the light beam.

Reflections are an abundant and sometimes confusing source of polarised light on land. Light reflected from shiny dielectric surfaces such as water, waxy leaves and some animal parts (Figure 2) has its e-vector parallel to that surface, while the others are refracted or absorbed. At a specific angle known as Brewster's angle (around 53° for water), the degree of polarisation reaches 100%. Reflection is in fact an example of coherent scatter. Incoherent particle scatter (Rayleigh scattering) is another widespread source of polarised light both in the sky, and underwater and at scatter angles of 90° in air, polarization may reach 100%, while underwater, due to multiple scattering events, the degree of polarisation rarely exceeds 50%.

These extended fields of polarised light, the celestial hemisphere and aquatic background space-light, can be viewed using sun glasses. At dawn or dusk, looking up into a clear blue